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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,641	10/27/2003	Deanna L. Kroetz	02307O-115611US	4011

20350 7590 09/17/2008

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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
09/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,641	KROETZ ET AL.	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *47 and 49* is/are allowed.

6)☒ Claim(s) *46, 48 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Summary of Action

2. The rejection of claims 46 and 48 under 35 U.S.C. 102(b) as being anticipated by Ichihara et al. (JP 07304755) is not maintained in light of the amendment/declaration(s) filed 06/02/08.

3. The rejection of claims 46 and 48 under 35 U.S.C. 102(e) as being anticipated by Blum et al. (US 5962455) is maintained for the reasons of record.

4. The rejection of claims 50-53 under 35 U.S.C. 103(a) as being unpatentable over Blum et al. (US 5962455) is maintained for the reasons of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 46 and 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Blum et al. (US 5962455).

Blum teaches use of compounds (e.g., RN 202472-67-1, RN 202472-68-2, RN 202472-69-3, RN 202472-70-6,etc…) or their salt, which reads on the instantly claimed compounds of the formula 1, for the treatment of the claimed cardiovascular disease such as hypertension or essential hypertension as well as congestive heart failure, wherein said compound is administered in dosage amounts of from about 0.1mg to about 140mg per kilograms of body weight per day and in various dosage forms including oral dosage form (abstract; column 1, line 39; column 1, line 45 thru column 3, line 15; column 7, line 51; column 8, line 52 thru column 10, line 62).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blum et al. (US 5962455).

The teaching of Ichihara or Blum has been discussed in above 35 USC 102 (e) rejection.

However, the prior art does not disclose the underlying pharmacological mechanism of said compounds in exhibiting the specific epoxide hydrolase enzymatic activity with "an IC50 of less than 500 μM or an IC50 of less than 17.8 μM". The fact that the applicant may have discovered a new pharmacological mechanism for same compound is not considered patentably distinctive over the prior art which are directed to the same therapeutic application (for the treatment of hypertension).

Thus, in absence of factual evidence or test indicating the criticality of the instant enzymatic activity, generally by showing that the claimed range of sHE inhibitor activity achieves unexpected results over the prior art, the examiner maintains that either Ichihara or Blum makes obvious the instant invention.

Allowable Subject Matter

7. The following is a statement of reasons for the indication of allowable subject matter: The prior art reference(s) alone or in combination (Ichihara et al. and Blum et al.) in which the

rejection of record is relied upon fail(s) to teach or suggest the use of compounds recited in Table I for the treatment of hypertension. Accordingly, claims 47 and 49 are allowed.

Response to Arguments

8. Applicant's arguments/declarations filed 06/02/2008 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that it is improper for the Office to ignore or disregard an express structural limitation set forth in both claims 46 and 48 "...wherein R^1 and R^3 are each independently selected from the group consisting of C_1-C_{20} substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic". Applicant asserts that the clause recited in claims 46 and 48 is an express structural limitation which limits the R^1 and R^3 substituents on both sides of the urea core to C_1-C_{20}, regardless of whether it is a substituted or unsubstituted alkyl, cycloalkyl, aryl, acyl, and heterocyclic.

This argument is not found persuasive. Unlike the applicant's argument, the reasonable interpretation of alternative expression recited in both Markush-type claims 46 and 48 refers to members as being selected from "C_1-C_{20} substituted or unsubstituted alkyl" alternative, "cycloalkyl" alternative, "aryl" alternative, "acyl" alternative or "heterocyclic" alternative. In other words, the applicant's interpretation of the clause recited in claims 46 and 48 as to "R^1 and R^3 substituents on both sides of the urea core to C_1-C_{20}" is in serious error. As discussed in the previous response (page 7, 1st paragraph of O.A. mailed 02/07/2008), there is no indication in the instant claims 46 and 48 that R^1 and R^3 must be essentially in C_1-C_{20}. Rather, the instant claims allow for inclusion of "cycloalkyl, aryl, acyl and heterocyclic" as R^1 and/or R^3 alternative

species. Thus, the examiner maintains that Blum's compounds read on the instant compounds represented by the structure formula depicted in claims 46 and 48 (when R1 and R3 are "aryl").

Applicant's argument in the response takes the position that the substituted benzylamine derivative compounds disclosed by Blum are unlikely to inhibit sEH activity rather than necessarily inhibit sHE because of the structural unrelatedness of human NPY1R and human sEH proteins and bulkiness of at least one of the substituents (i.e., the substituent that has more than 20 carbons). Applicant alleges that Exhibits submitted on June 02, 2008 and Dr. Bruce Hammock's Declaration submitted on June 13, 2006 and February 23, 2007 confirm that the substituted benzylamine derivative compounds of Blum are unlikely to inhibit the enzymatic activity of sEH.

This argument is not found persuasive. With respect to Dr. Hammock's Declaration, the examiner likes to point out that there is no conclusive statement or data showing that the compounds of Blum do not show any inhibitory activity of sHE. Rather, Dr. Hammock stated that the referenced compounds (e.g., compound RN 202472-69-3 and RN 202472-70-6) could be "mediocre activity" (see page 7 of Declaration filed 06/13/06). In other words, it is clear from Dr. Hammock's statement that the compounds of Blum possess some degree (little to moderate) of sEH inhibitor activity. Since the instant claims 46 and 48 do not specifically recite how much of sEH enzymatic activity is required to practice the claimed invention, the prior art directing the administration of the same compound in overlapping dosage amounts (see "0.001 μM/kg to about 100mg/kg body weight" in para. [0060] of the instant specification) inherently possessing therapeutic effect for the same ultimate purpose (e.g., the treatment of hypertension) as disclosed

by the applicant clearly anticipates the claimed invention even absent explicit recitation of underlying mechanism.

Even assuming arguendo that the certain degree of sHE enzymatic activity (for example much less with an IC50 of less than 500 μM or an IC50 of less than 17.8 μM as the applicant alleged) is critical for the claimed invention, generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it not inventive to discover the optimum or workable particle distribution percentage or concentration by routine experimentation.

Conclusion

9. Claims 47 and 49 are allowable.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614